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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/973,375	10/09/2001	Donald Gerald Stein	07157/239838 (5543-17)	5877

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/973,375	STEIN ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the interview summary (September 20, 2004) wherein Applicant's experiemntal results and their explanation of the results of allopregnanolone were presented, and Applicant's request for reconsideration of the rejection of the Final Office action April 21, 2004, **the finality of that action is therefore, withdrawn**.

Therefore, the rejection of claims 1-20 made under 35 U.S.C. 103(a) as being unpatentable over Gee et al. (Re. 35,517, of record) in view of Roof et al. (of record) further in view of Weinshenker et al. (5,068,226, of record) of record in the previous Office Action April 21, 2004 is withdrawn in favor of the new ground(s) of rejection(s) under 35 U.S.C. 102(b) below.

Thus, Applicant's Remarks (response) filed September 21, 2004, have been considered but are moot in view of the new ground(s) of rejections herein.

Currently, claims 1-20 are pending in this application.

Claims 1-20 are examined on the merits herein.

The following is the new ground(s) of rejection(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "a subject" renders these claims indefinite. The recitation "a subject" is not clearly defined in specification. One of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to those not excluded "a subject" would be, for example, that the term " subject " would be a single cell, an animal, a mammal, a human, any biological system, or even any non-biological system. Thus, one of ordinary skill in the art could not ascertain and interpret encompassed thereby.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13 and 15-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Roof et al., (*Molecular and Chem. Neuropathology*, 1997, vol.31, 1-11, of record).

Roof et al. discloses that progesterone has been shown to have neuroprotective effects following traumatic brain injury in rats, and/or in injured nervous system including the severity of postinjury cerebral edema. See the entire article especially abstract and introduction. Roof et al. particularly discloses the administration of progesterone to male

rat patents after suffering medical frontal cortex contusions, i.e., initial treatment of progesterone with a pharmaceutical carrier, oil, by injection, 4 mg/kg, was given 5 min post-injury and the remaining injections, 4 mg/kg, were given 6 hour post-injury and again once each 24-hours (see the last paragraph of page 3 to page 4 the 3rd paragraph), or the initial treatment after injury occurs at least within 2 hours of contusion (see page 6-7). Roof et al. also teaches that other agents or compounds such as vitamin E and methylprednisolone are known to be useful in the claimed method with progesterone (see page 3, lines 5-9).

Note that Roof et al. discloses that the effective amount of progesterone to be administered is in the range of 4 mg/kg, which is the instant claimed amount in claim 8 herein and also within the claimed effective amounts, about 1 μg/kg- 50 mg/kg, in claim 7 herein.

Given the fact that allopregnanolone is an old and well-known progesterone metabolite, which was necessarily produced in the patient's body upon ingestion of progesterone in the body (see "Steroid metabolism in humans" by Dobriner et al., e.g., page 48, PTO-892), Roof's steps are thus same as the instant method steps, administering progesterone which was necessarily converted to allopregnanolone in the patient's body upon ingestion, in the same amount to the same patient population. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

Note that the court ruled that the metabolite of loratadine called descarboethoxyloratadine or "DCL" was INHERENTLY anticipated by loratadine

(Claritin ™) because it was necessarily produced in the patient's body upon ingestion of Claritin ™. See Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003).

Moreover, Roof's method inherently decreases neurodegeneration in a patient following a traumatic injury to the central nervous system, as claimed herein since again Roof's method steps are same as the instant method steps, as discussed above.

Thus, Roof et al. anticipates Claims 1-13 and 15-20.

Claims 1-13 and 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Roof et al. (*Restoration Neurology and Neuroscience*, 1992, vol.4, 425-427, of record).

Roof et al. discloses that progesterone is useful in treating brain edema resulting from traumatic brain injury or following contusion injury in male and female rats. See the entire article especially abstract and introduction. Roof et al. particularly discloses the administration of progesterone with a pharmaceutical carrier, peanut oil, to male rat patents after suffering medical frontal cortex contusions, i.e., initial treatment of progesterone by injection, 4 mg/kg, was given 1 hour after contusion and the remaining injections, 4 mg/kg, were given 6, 24 and 48 hour post-injury (see the 3rd paragraph of page 426), or the initial treatment after injury occurs at least within 2 hours of contusion (see page 6-7).

Note that Roof et al. discloses that the effective amount of progesterone to be administered is in the range of 4 mg/kg, which is the instant claimed amount in claim 8

herein and also within the claimed effective amounts, about 1 μg/kg- 50 mg/kg, in claim 7 herein.

Given the fact that allopregnanolone is an old and well-known progesterone metabolite, which was necessarily produced in the patient's body upon ingestion of progesterone in the body (see "Steroid metabolism in humans" by Dobriner et al., e.g., page 48, PTO-892), Roof's steps are thus same as the instant method steps, administering progesterone which was necessarily converted to allopregnanolone in the patient's body upon ingestion, in the same amount to the same patient population, as discussed above. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). See also Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003).

Moreover, Roof's method inherently decreases neurodegeneration in a patient following a traumatic injury to the central nervous system, as claimed herein since again Roof's method steps are same as the instant method steps, as discussed above.

Thus, Roof et al. anticipates Claims 1-13 and 16-20.

Claims 1-7, 13 are 16-17 rejected under 35 U.S.C. 102(b) as being anticipated by Gee et al. (Re. 35,517, of record).

Gee et al. discloses that progesterone metabolites including the particular progesterone metabolite, allopregnanolone, are useful in a method for treating seizure disorders (see particularly col.4 lines 37-39; col.1 lines 17-21; Table 2 at col.13-14, ,).

Gee et al. also discloses that the beneficial effect of progesterone is related to the conversion of progesterone to the active metabolites including allopregnanolone since the metabolites and derivatives possess higher potency and efficacy than progesterone (see col.17 lines 29-35).

Note that seizures are known to be resulted from traumatic brain injury (see Hernandez et al., *Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal*, PTO-892).

Gee et al. also discloses the effective amounts of progesterone derivatives, either singly or *mixtures*, to be administered, i.e., 50 mg to 500 mg per dosage unit, and various known pharmaceutical carriers broadly in the compositions. See col.9 lines 16-25 and 32-62, col.10 lines 2-3, and claims 1 and 5.

Since a standard person weight is 70 kg, the claimed effective amount of about 1 μg/kg- 50 mg/kg, for example, 1 mg/kg X 70 kg =70 mg, within the Gee's range.

Thus, Gee's method steps are same as the instant method steps, administering the same compound in the same amount to the same patient population having seizures after traumatic brain injury. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3d. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001).

Thus, Gee et al. anticipates Claims 1-7, 13 are 16-17.

Claims 1-7 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Tauboll et al. (*Epilepsy Research*, (1993), 14(1), 17-30).

Tauboll et al. discloses that progesterone and the particular progesterone metabolite, 5α-pregnan-3α-ol-20-one (3α-OH-DHP, also known as allopregnanolone) with a pharmaceutical carrier, glycofurol, are useful in a method for treating epileptic seizure in animals such as cats (see abstract and the entire article).

Note that traumatic brain injury is known to cause epileptic seizure as discussed above (see Hernandez et al., *Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal*,).

Tauboll et al. also discloses the effective amounts of 3α-OH-DHP, to be administered, i.v. injection 1.0 mg/kg (see abstract), or (0.5-1.0 mg/ml) X (0.13-0.4 ml/kg) (see the left column of page 19), within the instant claimed range.

Thus, Tauboll's method steps are same as the instant method steps, administering the same compound in the same amount to the same patient population of those having seizures after traumatic brain injury. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3d. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001).

Thus, Tauboll et al. anticipates Claims 1-7 and 12-13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roof et al. or Gee et al. in view of Weinshenker et al. (5,068,226, of record).

The same disclosure of Roof et al. or Gee et al. has been discussed in the 102(b) rejection set forth above.

The prior art does not expressly disclose the employment of cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone.

Weinshenker et al. discloses that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone (see col.6 lines 20-32).

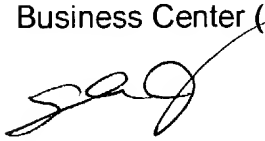
One having ordinary skill in the art at the time the invention was made would have been motivated to employ cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone since that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone according to Weinshenker et al.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
October 29, 2004